REMARKS

Claims 1-27 are pending in this application, with claims 14-25 standing withdrawn from consideration following a final restriction requirement. New claims 26 and 27, being dependent from claim 1, should be examined together with claims 1-13.

As noted in the Office Action, applicants have not previously supplied a certified copy of their priority application. Accordingly, enclosed herewith is a certified copy of India Patent Application No. 156/MAS/2003 filed February 28, 2003, and this submission should complete all remaining requirements of the claim for priority under 35 U.S.C. § 119.

The various grounds for rejecting the claims are traversed in the following discussion.

Rejections Under 35 U.S.C. § 112

The examined claims were rejected under the first paragraph of the statute, as failing to comply with the written description requirement. However, this paragraph does not pertain to claims, but establishes requirements for the specification. Applicants submit that their specification is entirely adequate for teaching those skilled in the art how to practice the claimed invention: applicants have provided examples of processes for preparing their claimed rabeprazole sodium Form Z from rabeprazole and from the crystalline form X of rabeprazole sodium. In addition, an example of a pharmaceutical composition containing the Form Z has been provided, along with a procedure for combining the ingredients.

Claims 1-10 stand rejected under the second paragraph of the statute, as being indefinite. The various grounds for the rejections are discussed below:

Claims 1 and 6-10 were identified as containing the trademark or trade name "rabeprazole." However, rabeprazole is not a trademark, but is the adopted "generic" name for the drug substance. Products containing rabeprazole sodium are being sold using the trademark "ACIPHEX." In the United States, uniform generic names are established for new drug substances by The United States Adopted Names (USAN) Council, which is co-sponsored by the American Medical Association, the United States

Pharmacopeial Convention, and the American Pharmacists Association; USAN works with the International Nonproprietary Name (INN) Programme of the World Health Organization and various national groups to establish global standardization and unification of drug names.

Claims 2-5 were held to lack antecedent basis for their limitations. However, applicants do not understand this rejection, as claim 1 is directed to a compound and each of its dependent claims 2-5 refers to "the compound of claim 1" (or of claim 2). The dependent claims define properties of the compound of claim 1.

Claim 6 has been amended to correct the typographical error that was identified in the Office Action.

Claim 4 was deemed to be incomplete, due to its reference to Fig. 1. However, this is a common technique for incorporating a particular X-ray diffraction pattern, which cannot be adequately described in words, into a claim. Examples of this style of claiming can be found in the following recently granted patents:

United States Patent No. 6,894,051 B1, claim 16
United States Patent No. 6,884,805 B2, claims 18 and 37
United States Patent No. 6,872,725 B2, claims 5, 10, and 12
United States Patent No. 6,831,091 B2, claims 2, 6, and 10
United States Patent No. 6,815,457 B1, claim 11
United States Patent No. 6,806,280 B1, claim 6
United States Patent No. 6,645,982 B2, claims 4 and 15.

As pointed out by the applicants (see paragraph 0032 of their published application: US 2004/0180935 A1), comparison of the entire X-ray diffraction pattern for rabeprazole sodium Form Z with the pattern for an unknown substance is the preferred method for determining substantial identity of the substances.

The various rejections under 35 U.S.C. § 112 cannot be supported, and therefore they should not be maintained, upon reconsideration.

Rejection Under 35 U.S.C. § 102

All of examined claims 1-13 were rejected under paragraphs (a), (b), and (e) of the statute, as being anticipated by JP 2001-39975 ("Takashi"), U.S. Patent 5,045,552 to Souda et al., and WO 03/082858 ("Reddy et al."). However, none of these documents discloses the applicants' claimed subject matter.

The Japanese patent application referred to as Takashi appears to relate to a crystalline form of rabeprazole sodium. The only X-ray diffraction pattern in the application that corresponds to a crystalline substance is on page 9 of the application, appearing to be Fig. 1. This pattern does not correspond to the applicants' Figure 1 diffraction pattern. Additionally, the thermal analysis information provided in the figures on page 11 of the Japanese application does not correspond with the applicants' Figure 2 thermal analysis information. Thus, the Japanese application cannot be considered to anticipate any of the present claims.

The Souda et al. patent, in its Example 33, appears to show preparation of rabeprazole sodium from rabeprazole. This preparation culminates in a precipitation of rabeprazole sodium crystals from an ethanol solution, by the addition of ethyl ether. There is no X-ray diffraction pattern in the patent, but the product is said to decompose upon heating to 140-141°C, which is quite different from the thermal analysis properties of the applicants' product; see the melting point of 224-230°C described in paragraph 0033 of the applicants' published application US 2004/0180935 A1. This patent cannot anticipate any of the present claims, as its example prepared a different product.

WO 03/082858 discloses two crystalline forms (Form X and Form Y) of rabeprazole sodium. However, comparison of the X-ray diffraction patterns (Figs. 1 and 2) from this publication with the applicants' Figure 2 reveals considerable differences. Comparison of the thermal analysis information (Figs. 3 and 4) from the publication with the applicants' Figure 2 also reveals considerable differences. Therefore, this publication cannot anticipate any of the presently examined claims.

The rejections under 35 U.S.C. § 102 have no basis in fact, since anticipation requires that a reference document discloses each and every element of a claim. See

Ex parte Levy, 17 USPQ2d 1461 (Bd. Pat. App. and Interf. 1990). These rejections should therefore not be maintained, upon reconsideration.

Rejection Under 35 U.S.C. §103(a)

Claims 1-13 were rejected under this statute as being rendered obvious by a combination of teachings from the three patent documents discussed above, combined with five additional non-patent publications:

a) J. Halebian et al, "Pharmaceutical Applications of Polymorphism," *Journal of Pharmaceutical Sciences*, Vol. 58, No. 8, pages 911-929, August 1969;

b) A. M. Rouhi, "The Right Stuff," *Chemical and Engineering News*, Vol. 81, No. 8, pages 32-35, February 24, 2003;

c) *United States Pharmacopeia 23, National Formulary 18*, 1995, pages 1843-1844;

d) Brittain et al., *Polymorphism in Pharmaceutical Solids*, Marcel Dekker, Inc., New York, 1999, pages 228-361; and

e) M. Eagleson, Trans., *Concise Encyclopedia Chemistry*, Walter de Gruyter, New York, 1994, pages 872-873.

Guidance for obviousness rejections has been provided by M.P.E.P. § 706.02(j), as follows:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

Nothing in the cited documents, or any combination of the cited documents, teaches or suggests anything relating to the applicants' claimed Form Z of rabeprazole sodium. The cited patent documents, as discussed above, teach no more than the existence of other polymorphic forms of the compound. The non-patent cited

documents all are indications of the present uncertainty in the relevant art concerning polymorphism, and do not add anything substantive to the teachings of the patent documents.

Applicants are enclosing a copy of the article by A. Goho, "Tricky Business," *Science News*, Vol. 166, No. 8, pages 122-123, August 21, 2004, as reprinted from the publication's website in eight pages. This article summarizes the state of the art and clearly indicates three truths in the field of polymorphism:

1) It is not possible to predict whether a given compound exhibits polymorphism;

2) If a compound exhibits polymorphism, it is not possible to predict how many polymorphic forms will be found; and

3) There is no standard procedure for preparing a polymorphic form of any compound.

Particularly relevant is the discussion beginning on the fifth page of the reprint, under the heading "Forecasting," which (in the fourth paragraph of that section) quotes an expert in the field as stating, "Right now, you can't predict polymorphs, and you can't predict their properties."

Given the uncertainty in the field, and the fact that the cited documents contain no prediction of the existence of the claimed rabeprazole sodium Form Z, there can be no *prima facie* case for obviousness. The combined teachings of the cited documents amount to no more than an invitation to perform experiments, and "obvious to try" has long been regarded as an insufficient basis for an obviousness rejection. See, for example, *The Gillette Company v. S. C. Johnson & Son Inc.*, 919 F.2d 720 (also 16 USPQ2d 1923), Fed.Cir. 1990, where the court stated at 725:

> Johnson takes the position that, at most, the substitution suggested by Gillette may be "obvious to try." As we recently explained, [a]n "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. In re Eli Lilly & Co., 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed.Cir.1990). However, we have consistently held that "obvious to try" is not to be equated with obviousness under 35 USC 103. See O'Farrell, 853 F.2d at 903,

7 USPQ2d at 1680; Hybritech, 802 F.2d at 1380, 231 USPQ at 91; Jones v. Hardy, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed.Cir.1984).

There is no technical information in any of the five non-patent documents, relating to rabeprazole sodium. Therefore, the deficiencies of the three patent documents (discussed above in connection with the anticipation rejection) are not altered by the combination of teachings from the non-patent documents. Obviousness has not been established, and the rejection should now be withdrawn.

Double Patenting Rejection

The examined claims stand provisionally rejected under the judicially created doctrine of double patenting, asserted as being rendered obvious by a combination of claims 1-6, 8-13, and 16 from U.S. Patent Application No. 10/505,825, with the five non-patent documents that were cited in connection with the obviousness rejection, discussed above. The cited copending application is the U.S. national phase filing of the international application that was published as WO 03/082858.

As noted above in connection with the anticipation rejection, the PCT publication relates to crystalline forms X and Y of rabeprazole sodium, and these forms are not the same as the present applicants' Form Z. Note particularly the melting ranges given for Form X (140-150°C), Form Y (160-170°C), and Form Z (224-230°C), which comparison was made in the present application. This application also has the X-ray diffraction pattern peaks for each of these polymorphic forms listed in a tabular format, and a casual inspection of the tables is sufficient to determine that the forms are not equivalent.

Since none of the documents, nor any possible combination of teachings from the documents, discloses or predicts the existence of the presently claimed Form Z of rabeprazole sodium, there is no plausible case for obviousness and double patenting will not be a possibility. This rejection should not be maintained.

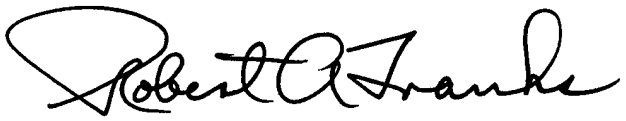
CONCLUSION

Examined claims 1-13, and new claims 26 and 27, appear to be in a proper form for their allowance, and therefore reconsideration of the rejections and an early

notification of allowance is respectfully requested. Should any minor matters remain to be resolved before disposition of the application, please contact the undersigned to arrange for a telephonic or personal interview.

Any additional fees that are due in connection with this submission should be charged to Deposit Account 50-3221.

Respectfully submitted,



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Tricky Business

The crystal form of a drug can be the secret to its success

Alexandra Goho

In one of Kurt Vonnegut's science fiction novels, a scientist creates a form of ice that doesn't melt until it reaches 114.4°F. Called Ice-9, this imaginary crystal takes over the world, as all of Earth's waters, and life itself, freeze solid. What endows Ice-9 with such unusual properties is the unique configuration of the stacked water molecules. Although Ice-9 of *Cat's Cradle* (1963, Holt, Rinehart and Winston) is pure fantasy, the concept of a molecule assuming multiple crystal structures—or polymorphs—is real, and the consequences can be dramatic. One polymorph of carbon provides black and slippery graphite, another is hard, transparent diamond. A blue pigment used in ink-jet printers has either a red or green tint, depending on the pigment's crystal structure. Even crystallized cocoa butter has different polymorphs; some cause the chocolate to melt in your mouth more quickly than others.

In recent years, the pharmaceutical industry has increasingly focused its attention on polymorphs. There's plenty of incentive. The precise arrangement of molecules within the crystal of a drug determines how fast it dissolves in the body and how much enters the bloodstream. Polymorphs of a drug differ in properties that affect its shelf life or ease of manufacture. A newly discovered polymorph may turn out to be a more effective and convenient than the original product.

TRUE COLORS. The organic compound dubbed ROY can adopt six different crystal structures, or polymorphs, ranging from yellow needles to orange-red plates. ROY is currently the world record holder for having the largest number of fully characterized polymorphs.
Yu

The Food and Drug Administration requires all companies to register the precise polymorph of any drug that they produce. Pharmaceutical manufacturers also have to demonstrate that each polymorph is stable and can be reproduced reliably. Otherwise, it would be hard to set a drug's effective dosage. "The FDA has very strict regulations on this," says Jerry Atwood of the University of Missouri-Columbia.

Regulations aside, drug companies are becoming increasingly aware that different polymorphs can translate into more or less profit. Because each polymorph is legally defined as a unique, patentable composition of matter, a company that develops a new drug will patent all the polymorphs that it has discovered and produced.

That, however, affords the patent holder only limited business protection. Because the science behind polymorphs remains murky, there's no guarantee that a competitor won't discover a new polymorph of the drug that's better than the patented ones.

The world of polymorphs also opens up complicated business strategies. For example, when a patent is set to expire, a company might have other patents related to a drug's polymorphs that make it difficult for competitors to produce generic versions.

Situations such as these have fueled intense litigation over the years. "The polymorph issue is so important to the pharmaceutical industry," says Atwood. "We're talking about multibillion-dollar drugs. Ultimately, it comes down to a hard legal battle."

It also comes down to fundamental chemistry. Polymorphism has elicited enough excitement and fear in the drug business that a growing number of researchers in academia and in private companies are taking a closer look at how crystals grow, and what these scientists discover could shape an entire industry.

Disappearing act

Emblematic of the importance of polymorphs is the cautionary tale of ritonavir, the AIDS drug made by Abbott Laboratories. Introduced in 1996, the drug had been on the market for 18 months when suddenly, during manufacturing, chemical engineers detected a previously unknown polymorph. No one knew what had caused the change, but the scientists discovered that the new polymorph was thermodynamically stabler than the drug in its original form. The Abbott team couldn't find a way to stop formation of the new polymorph. Within a few days of its discovery, this new polymorph was dominating the product coming off the lines, says Sanjay Chemburkar, one of the Abbott chemists involved in the situation.

Although the two polymorphs shared a chemical formula, their structural dissimilarity made a difference to patients. The second form was only half as soluble as the first, so patients taking prescribed doses wouldn't get enough of the drug into their bloodstreams. Abbott pulled ritonavir from the market.

"The company went on a crash program to try to get their [original] polymorph back," says Atwood. Abbott eventually succeeded in producing the first form again, but it could not make the polymorph reliably and kept getting mixtures of the two forms. The company finally decided to reformulate the drug in the second polymorphic form as a liquid gel capsule containing the predissolved drug. Unlike the original formulation of the drug, the gel capsules require refrigeration.

"Abbott lost a lot of money over this," says Allan Myerson of the Illinois Institute of Technology in Chicago. The company spent hundreds of millions of dollars trying to recover the first polymorph and lost an estimated $250 million in sales the year the drug was withdrawn.

Cases such as this aren't routine, but they're common enough for drug companies to be concerned about the surprises that polymorphism can bring, says Myerson.

Screening for polymorphs early on is always best, says Patrick Stahly. He's the chief operating officer at SSCI, a contract research laboratory in West Lafayette, Ind., that specializes in crystal screening and analysis. Even so, drug companies often wait until late in the development process before thoroughly screening for polymorphs. "We've had clients come to us in the middle of human clinical trials after discovering their drug had two different polymorphs," says Stahly. Such a company has to regain control over its manufacturing

process and start the trials over using a single polymorph.

That experience underscores one way that companies can get bitten by polymorphism. There are other potential pitfalls as well.

Consider ranitidine hydrochloride, the anti-ulcer drug owned by the drug giant GlaxoSmithKline and known by millions as Zantac. In the mid-1990s, as the patent on the drug was approaching expiration, other companies began gearing up to market cheaper, generic versions. By marketing drugs that have gone off patent, generics manufacturers skip human trials, the most expensive part of the drug-development process.

However, GlaxoSmithKline—which was simply Glaxo at the time—had in its pocket a patent on a second polymorph of the drug. The company discovered that second form early in the processing of the first form. Glaxo didn't receive a patent on the second form until nearly 7 years after receiving the initial drug patent. Because the second form was easier to manufacture, it became the active ingredient in Zantac.

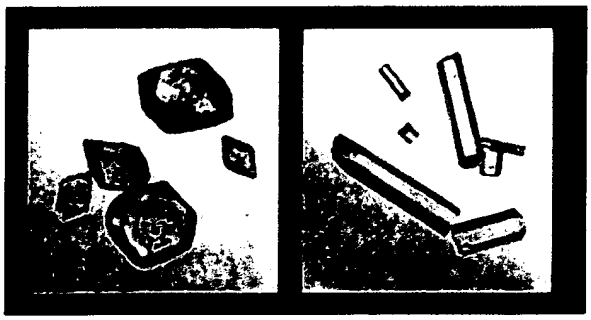
Although other companies were legally permitted to make and sell generic versions of the first polymorph of ranitidine hydrochloride, they had to figure out how to make it without any contamination from the second, whose patent protection remained in force. This kept the generic companies products off the market for several years.

"Zantac was the largest-selling drug in the world," says Joel Bernstein of Ben-Gurion University of the Negev in Beer Sheva, Israel. Bernstein was an expert witness for Glaxo when a dispute over its original patent went to court. Glaxo was making $10 million in sales each day on its ulcer treatment, so every day it retained control over its drug was significant.

Crystal fate

The conventional approach to finding polymorphs begins with old-fashioned crystallization experiments. First, dissolve the drug in a solvent. Next, cool the solution or evaporate the solvent, coercing the drug molecules to stick together to form crystals. Varying the temperature of the solution and using different solvents are among the long-used tricks for getting the molecules to stack in different geometries.

Trying to discover new polymorphs in the lab can be frustrating. "Sometimes they show up, sometimes they don't," says Adam Matzger of the University of Michigan in Ann Arbor. "There is very little in the way of new approaches to finding polymorphs."



POLYMER RELIEF. Growing crystals of the pain-relieving drug acetaminophen on different polymer surfaces will yield different crystal structures. One polymer gives rise to tiny prisms (left); another, miniature monoliths (right). Z. Tolstyka

In search of ideas, researchers have been exploring factors other than temperature and solvent that might influence crystallization and produce polymorphs. For instance, SSCI is investigating a technique developed by Myerson. Two years ago, he and his colleagues found that intense pulses of near-infrared light could affect the crystallization of the amino acid glycine. When the light was linearly polarized, so that its

electric field vibrated in one direction, the crystal grew as one polymorph; when the light was circularly polarized, so that the electric field rotated, it induced a second polymorph.

Myerson suspects that the electric field generated by the light influences how the glycine molecules arrange themselves as they aggregate into small clusters early in the crystallization process.

The instructions for growing into a particular type of polymorph are imprinted on the cluster by the time it reaches a critical size containing tens to hundreds of molecules. Once these nuclei form, the "fate of the system has been decided," says Michael Ward of the University of Minnesota in Minneapolis.

Different packings of molecules lead to nuclei of different sizes, which in turn yield different polymorphs. So, Ward wondered whether confining a dissolved compound to a given space would limit the size of a nucleus that could form and force the molecules to pack in a specific polymorphic arrangement. As they reported in the March 24 *Journal of the American Chemical Society*, he and his colleagues tested this hypothesis by growing crystals within porous materials.

The Minnesota team turned to blocks of polymer with cylindrical pores 30 nanometers in diameter. To this material, the researchers added a solution of an organic chemical commonly used in the manufacture of pharmaceuticals. This compound, dubbed ROY, is currently the world record holder for having the most—six—fully characterized polymorphs. However, Ward and his colleagues found that only one form of ROY crystallized inside the pores.

Ward notes that the fine details of surfaces also play a role in crystallization. Think of rock candy. "When you dissolve sugar in water and put a stick in the container, where does the candy grow? On the stick," he says.

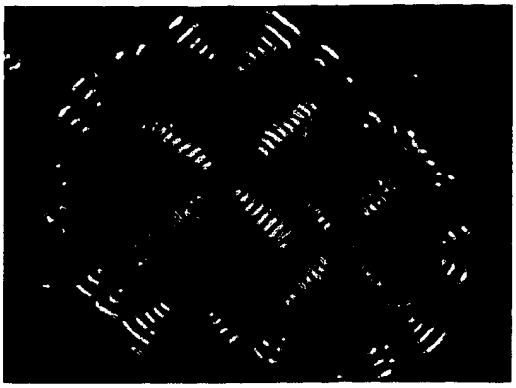
Matzger, for one, has found that growing crystals of the same compound on different polymer materials can produce different polymorphs. The Michigan group crystallized the pain-relieving drug acetaminophen, which is known to have two polymorphs, on 84 different polymer materials. They found that certain materials, such as nylon and polyvinyl chloride—the plastic used in plumbing—induced one form to grow, while other polymers, such as cellulose, favored the other form.

Next, the researchers did a similar experiment with carbamazepine, an antiepileptic drug with three known crystal structures. Not only did all three polymorphs show up, but also a new and previously unknown polymorph grew on 4 of the 84 polymers. Matzger speculates that the precise way in which a polymer's atoms are arranged near the surface could favor the growth of certain polymorphs.

While pharmaceutical firms might use strategies like these to discover new polymorphs, once a company lands on a desirable crystal form of a drug, it faces other challenges. To make large quantities, researchers often seed batches of the dissolved drug with a small grain of the desired polymorph, expecting the grain to nucleate the growth of much larger crystals of the same polymorph.

That strategy usually works, but sometimes it doesn't.

"The engineers will often say to me: 'The polymorphism of this drug is out of control. I seed with this crystal and I get something else,'" says pharmaceutical chemist Lian Yu.



BAD SEED. Two different polymorphs of the sugar mannitol were detected with a spectral-imaging technique. The two crystal structures scatter radiation differently, producing a unique pattern of black and white bands. The image shows how one polymorph of mannitol (inner pattern) can cause a second polymorph (outer pattern) to grow on its surface. J. Am. Chem. Soc.

While working at Eli Lilly and Company in Indianapolis, Ind., Yu discovered that the surface of one crystal structure sometimes induces a different polymorph. In the May 28, 2003 *Journal of the American Chemical Society*, Yu describes an experiment in which he used a polymorph of the sugar mannitol to seed a dissolved solution of the sugar. The polymorph that started forming on the surface of that crystal was a different one altogether.

Yu, who is now at the University of Wisconsin–Madison, suspects that this process could be at the heart of many incidents, such as Abbott's ritonavir saga, in which researchers at drug-manufacturing plants suddenly find they can no longer grow the polymorph they want. Some unrecognized change in the manufacturing process might have altered whether the growing crystals model themselves after their seed crystals.

Forecasting

In 1965, a Chicago microscopist named Walter C. McCrone stated the following maxim regarding the art of crystal growing: "The number of forms known for a given compound is proportional to the time and money spent in research on that compound."

Consider ROY. It took Yu and his colleagues many years to produce all six forms, which they first reported in 2000. The colorful diversity of the different crystal structures—which range from red needles to orange plates to yellow prisms—and the fact that they all form at room temperature "really has captured the imagination of the community," says Yu.

Other compounds, however, do not support McCrone's rule. Aspirin, for example, has been crystallized by the tons for decades under many different conditions, and yet only one crystal form has ever emerged, says Sally Price at University College London. "People are fairly confident that there aren't any more to be found," she says.

Yet without extensive studies, there is no way to entirely discount the possibility that some sets of conditions could lead to polymorphs of aspirin. "Right now, you can't predict polymorphs, and you can't predict their properties," says Atwood.

Such forecasting might be possible in the future. Last fall, Price and her collaborators launched a multimillion-dollar research initiative to develop computer software tools that consider the arrangement of atoms within a compound to predict whether that compound is likely to take on different crystal structures and, if so, approximately how many.

A company might use such predictions to find that one of its drug molecules has other stable polymorphs. If so, the company would aggressively search for those polymorphs. The

predicted crystal structures would also give researchers ideas for methods to produce the polymorphs in the lab.

Alternatively, the predictions might suggest that the polymorph in hand is the stablest form and that other forms are unlikely to arise. The company could then save the time and money that would otherwise be spent on unnecessary screening experiments.

At the moment, Price says her team can make predictions only for very simple molecules. "Most pharmaceuticals are far more complicated," she says. It could be a decade before such computer predictions can be applied to drug development. In the meantime, the specter of sudden polymorphism will remain a fact of life for pharmaceutical firms.

If you have a comment on this article that you would like considered for publication in *Science News*, send it to editors@sciencenews.org. Please include your name and location.

References:

Bernstein, J. 2002. *Polymorphism in Molecular Crystals.* New York: Oxford University Press.

Chemburkar, S.R., *et al.* 2000. Dealing with the impact of ritonavir polymorphs on the late stages of bulk drug process development. *Organic Process Research and Development* 4(September):413-417.

Childs, S.L. . . . and G.P. Stahly. 2004. A metastable polymorph of metformin hydrochloride: Isolation and characterization using capillary crystallization and thermal microscopy techniques. *Crystal Growth and Design* 4(May):441-449.

Garetz, B.A., J. Matic, and A.S. Myerson. 2002. Polarization switching of crystal structure in the nonphotochemical light-induced nucleation of supersaturated aqueous glycine solutions. *Physical Review Letters* 89(Oct. 21):175501. Abstract available at http://link.aps.org/abstract/PRL/v89/e175501.

Ha, J.-M. . . . and M.D. Ward. 2004. Polymorph selectivity under nanoscopic confinement. *Journal of the American Chemical Society* 126(March 24):3382-3383.

Lang, M., A.L. Grzesiak, and A.J. Matzger. 2002. The use of polymer heteronuclei for crystalline polymorph selection. *Journal of the American Chemical Society* 124(Dec. 18):14834-14835.

Price, S.L. 2004. The computational prediction of pharmaceutical crystal structures and polymorphism. *Advanced Drug Delivery Reviews* 56(Feb. 23):301-319. Abstract available

at http://dx.doi.org/10.1016/j.addr.2003.10.006.

Yu, L. 2003. Nucleation of one polymorph by another. *Journal of the American Chemical Society* 125(May 28):6380-6381.

Yu, L., *et al.* 2000. Thermochemistry and conformational polymorphism of a hexamorphic crystal system. *Journal of the American Chemical Society* 122(Feb. 2):585-591.

Further Readings:

Davey, R.J. 2003. Pizzas, polymorphs and pills. *Chemical Communication* 13(June 12):1463-1467. Available at http://dx.doi.org/10.1039/b303125j.

Dunitz, J.D., and J. Bernstein. 1995. Disappearing polymorphs. *Accounts of Chemical Research* 28(April):193-200.

Grzesiak, A.L. . . . and A.J. Matzger. 2003. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. *Journal of Pharmaceutical Sciences* 92(November):2260-2271. Abstract available at http://dx.doi.org/10.1002/jps.10455.

McCrone, W.C. 1963. Polymorphism. In *Physics and Chemistry of the Organic Solid State*, D. Fox, M.M. Labes, A. Weissberger, eds. New York: Interscience Publishers.

Mitchell, C.A., L. Yu, and M.D. Ward. 2001. Selective nucleation and discovery of organic polymorphs through epitaxy with single crystal substrates. *Journal of the American Chemical Society* 123(Nov. 7):10830-10839.

Price, C.P. . . . and A.J. Matzger. 2003. Maize 1: A trimorphic azo pigment. *Crystal Growth and Design*. 3(November):1021-1025.

Price, C.P. . . . and A.J. Matzger. 2002. Polymorphism of nabumetone. *Crystal Growth and Design* 2(November):501-503.

Vonnegut, K. 1963. *Cat's Cradle*. New York: Holt, Rinehart & Winston.

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